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09/971,776	10/04/2001	Aaron Gershon Filler	GJE-06FD3	3171

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EXAMINER	
WHITEMAN, BRIAN A	
ART UNIT	**PAPER NUMBER**
1635	6

DATE MAILED: 07/01/2002

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/971,776	Applicant(s) FILLER ET AL.	
	Examiner Brian Whiteman	Art Unit 1635	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____ .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 1-17 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 1-17 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☒ Certified copies of the priority documents have been received in Application No. 08/211,041 .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449) Paper No(s) 5 .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

DETAILED ACTION

Non-Final Rejection

Claims 1-17, to which the following grounds of rejection are applicable, are pending examination.

Priority

Acknowledgment is made of applicant's claim for foreign priority under 35 U.S.C. 119(a)-(d). The certified copy has been filed in parent Application No. 08/211041, filed on 16 March 1994.

Claim Objections

Claim 16 is objected to under 37 CFR 1.75(c), as being of improper dependent form for failing to further limit the subject matter of a previous claim. Applicant is required to cancel the claim(s), or amend the claim(s) to place the claim(s) in proper dependent form, or rewrite the claim(s) in independent form. By excluding the nucleic acid of the agent in claim 1, claim 16 fails to further limit the subject matter of the previous claim.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-17, as best understood, are readable on a genus of a gene delivery vector comprising inorganic particles to which are bound a cell-binding component and a nucleic acid, wherein the genus of the cell-binding component and the binding of uncoated inorganic particles to its components are not claimed in a specific biochemical or molecular structure that could be

envisioned by one skilled in the art at the time the invention was made are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The specification contemplates production of a species of a gene delivery vector comprising ferrite particles bound to a target polypeptide molecule (e.g. wheat germ agglutinin, transferrin, antibody or antibody fragment), a nucleic acid and a nucleic acid binding protein, wherein the main property of the vector is binding the components to the ferrite particles. The as-filed specification provides sufficient description of a species of a gene delivery vector composed of a mixture of ferrous and ferric chloride salt with a polymeric coating, which covalently binds to a target polypeptide molecule and a nucleic acid, and a nucleic acid binding protein.

Furthermore, the as-filed specification further provides description of a species of a gene delivery vector produced by the preparation of a mixture of ferrous and ferric chloride, wherein the final product gives desirable homogeneity and avoidance of water-soluble materials, and contemplates that the disclosed composition provides sufficient description for one skilled in the art to envision a representative number of species of the genus of polymeric coated ferrite particles bound to a target polypeptide molecule, a nucleic acid, and a nucleic acid binding protein. The specification does not provide disclosure of a gene delivery vector comprising a target polypeptide molecule, nucleic acid, and a nuclease inhibitor (e.g. Group 3 ion).

However, it is apparent that on the basis of applicant's disclosure, an adequate written description of the invention defined by the claims requires more than a mere statement that it is

part of the invention and reference to potential methods and/or molecular structures of molecules that are essential for the genus of cell-binding components and/or gene delivery vector additionally comprising a nuclease inhibitor and/or what binds uncoated ferrite particles to cell-binding components, a nucleic acid, and a nucleic-binding protein as claimed; what is required is the knowledge in the prior art and/or a description as to the availability of a representative number of species of biochemical or molecular structures of cell-binding components, nuclease inhibitors, and/or final products of a gene-delivery vector that must exhibit the disclosed biological functions as contemplated by the claims.

It is not sufficient to support the present claimed invention directed to a genus of a gene-delivery vector comprising inorganic particles to which are bound a cell-binding component, nucleic acid and nucleic acid binding protein by giving examples of a ferrite oxide or salt coated with dextran to which a target polypeptide molecule, nucleic acid, and a nucleic acid binding protein are covalently bound. The claimed invention as a whole is not adequately described if the claims require essential or critical elements, which are not adequately described in the specification and which is not conventional in the art as of applicant's effective filing date. Claiming unspecified cell-binding components and/or functional groups thereof, and/or a genus of a gene delivery vector that must possess the biological properties as contemplated by applicant's disclosure without defining what means will do so is not in compliance with the written description requirement. Rather, it is an attempt to preempt the future before it has arrived. (See *Fiers v. Revel*, 25 USPQ2d 1601 (CA FC 1993) and *Regents of the Univ. Calif. v. Eli Lilly & Co.*, 43 USPQ2d 1398 (CA FC, 1997)). Possession may be shown by actual reduction to practice, clear depiction of the invention in a detailed drawing, or by describing the

invention with sufficient relevant identifying characteristics such that a person skilled in the art would recognize that the inventor had possession of the claimed invention. Pfaff v. Wells Electronics, Inc., 48 USPQ2d 1641, 1646 (1998). The skilled artisan cannot envision the detailed structure of a genus of the claimed and/or that must exhibit the contemplated biological functions, and therefore, conception is not achieved until reduction to practice has occurred, regardless of the complexity or simplicity of the structures and/or methods disclosed in the as-filed specification. Thus, in view of the reasons set forth above, one skilled in the art at the time the invention was made would not have recognized that applicant was in possession of the claimed invention as presently claimed.

Claims 1-17, as best understood, are rejected under 35 U.S.C. 112, first paragraph, because the specification is enabling only for claims limited to: 1) A gene delivery vector comprising ferrite particles having a polymeric coating to which a target polypeptide molecule (e.g. wheat germ agglutinin, transferrin, antibody or antibody fragment), a nucleic acid and a nucleic acid binding protein are covalently bound. The specification does not reasonably provide enablement for the presently pending claims encompassing any and/or all other gene delivery vectors comprising inorganic particles to which are bound an unspecified cell-binding component, a nucleic acid. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

> Factors to be considered in determining whether a disclosure would require undue experimentation have been summarized in In re Wands, 858 F.2d 731, 8USPQ2d 1400 (Fed. Cir. 1988). They include (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claims.

Specifically, since the claimed invention is not supported by a sufficient written description (for possession of a genus of a gene delivery vector comprising inorganic particles to which are bound a cell-binding component, and a nucleic acid), particularly in view of the reasons set forth above, one skilled in the art would not have known how to use and make the claimed invention so that it would operate as intended, e.g. function as a nucleic acid delivery vector or as a drug carrier.

Furthermore, the as-filed specification does not teach how to use the gene delivery vector comprising of uncoated ferrite particles to a target polypeptide molecule and a nucleic acid.

The specification teaches how to make a gene delivery vector, comprising polymeric coated ferrite particles covalently bound to a target polypeptide molecule, a nucleic acid and a nucleic acid binding protein. Unlike polymeric-coated (e.g. dextran-coated) ferrite particles, there is apparently no covalent attachment of a nucleic acid and a nucleic acid binding protein to uncoated ferrite particles. In the absence of covalent attachment, one would suspect that much, if not all, of the biologically active materials would dissociate from the endocytotic particles. In addition, the specification does not provide sufficient guidance for making and using inorganic particles, which additionally comprise of a nuclease inhibitor, as recited in claims 9-10.

The specification also does not provide guidance for using the gene delivery vector comprising uncoated ferrite particles to which a target polypeptide molecule and a nucleic acid; wherein, the nucleic acid is bound via a complementary sequence linked to the particles. The specification does not provide guidance as to how a complementary sequence coupled to the gene delivery vector functions as a whole after it is transfected into a cell.

In addition and as to claims encompassing the use of any DNA for therapeutic applications, the specification states that, "experiments have been carried out by the applicant demonstrating a surprising efficiency for the uptake of particles after intramuscular injection." If the claimed particles were injected into muscle tissue, which allegedly is less efficient at degrading exogenous nucleic acids, particle uptake would still be expected to be limited to the few cells adjacent to the injection site. If the nucleic acid is expressed only transiently, there is no indication of how long expression can be expected to persist. Cotton et al. teaches that receptor-mediated gene delivery is limited by retention of the endocytosed DNA in the endosome (Applicant's IDS, AP, pg. 6094). The specification does not provide any means of circumventing this problem when using the gene delivery vector. Thus, one would expect that a significant portion of the delivered nucleic acid would be degraded in the endosome before nucleic acid expression could occur. It is not clear whether any DNA escaping the endosome would be stably incorporated into the host genome, or in what percentage of cells this can be achieved. Furthermore, the specification cites an *in vivo* experiment showing that "the particles are ingested by human macrophages, T-cells, and osteogentic sarcoma cells, and that there is a slow clearance of the particles from the blood stream in a rabbit, with 25% of the injected dose remaining in the circulation after four hours." The specification does not provide guidance for how this experiment correlates to a therapeutic treatment of a patient. Thus, one skilled in the art could not predict with a reasonable degree of certainty that the claimed gene delivery vector could be used successfully for a therapeutic use, especially since there are no examples of successful examples of therapy or gene therapy in the as-filed specification and/or in the prior

art. If so, it would still require a considerable amount of experimentation to develop a method of using the gene delivery vector for use in therapy or in gene therapy to treat a patient.

The specification does not provide sufficient guidance and/or factual evidence demonstrating a reasonable correlation between the disclosure including the subject matter being sought in the claims wherein a composition comprising a gene delivery vector, comprising a ferrite oxide or salt having a polymeric coating to which a target polypeptide molecule and a nucleic acid are covalently bound can be used for gene therapy, particularly given all of the reasons set forth above. Furthermore, and with respect to claims directed to any pharmaceutical compositions useful for gene therapy and directed to any therapeutic treatment of a patient; the state of the art in 1998, exemplified Anderson et al., *Nature*, Vol. 392, pp. 25-30, April 1998, displays major consideration for any gene transfer and/or DNA therapy protocol involve issues that include:

1) The type of vector and amount of DNA constructs to be administered,

2) The route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site;

3) The trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and

4) What amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (IDS, Anderson, *Nature*, Vol. 392, pp. 25-30, April 1998).

In addition, all of these issues differ dramatically based on the specific vector used, the route of administration, the animal being treated, therapeutically effective amount of the DNA, and the disease being treated.

Anderson indicates that the state of the art before 1998, and teaches that gene therapy is a powerful new technology that still requires several years before it will make a noticeable impact on the treatment of disease, and that several major deficiencies still exist including poor delivery systems, both viral and non-viral, and poor gene expression after genes are delivered (pp. 25-30).

Anderson further teaches that the reason for the low efficiency of gene transfer and expression in human patients is that we still lack the basis understanding of how vectors should be constructed what regulatory sequences are appropriated for which cell types (page 30, column 1, last paragraph). Furthermore, Verma, (IDS, *Nature*, Vol. 389, pages 239-242, 1997), indicates that factors including the nature of the diseases and/or disorders, the nature of a DNA and/or target tissue, and a delivery system and/or amounts of the DNA complexes employed in the delivery system that would generate a therapeutic effect *in vivo* must be considered for any gene therapy method to be successful (page 238, columns 1 and 2).

As a result, it is not apparent how one skilled in the art determines, without undue experimentation, which of the claimed pharmaceutical compositions generates a therapeutic effect, how is it apparent as to how one skilled in the art, without any undue experimentation, practices any nucleic acid therapy method as contemplated by the claims, particularly given the unpredictability of nucleic acid therapy as a whole and/or the doubts expressed in the art of record.

In conclusion, the as-filed specification and claims coupled with the state of the art at the time the invention was made only provide sufficient guidance and/or evidence to reasonably enable 1) listed above, because given that gene therapy wherein any carrier is employed to correct a disease or a medical condition in any mammal was unpredictable at the time the invention was made, and given the lack of sufficient guidance as to a gene therapy effect produced by any of the gene delivery vectors cited in the claims, one skilled in the art would have to engage in a large quantity of experimentation in order to practice the claimed invention based on the applicant's disclosure and the unpredictability of gene therapy.

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter, which the applicant regards as his invention.

Claims 1, 12, 13, 15, 16, and 17 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 recites, "**adapted** to deliver a nucleic acid to a cell." The claim does not defined how the agent is **adapted** to deliver a nucleic acid to a cell.

Claim 12 recites, "nucleic acid is bound via **complementary sequence** linked to the particles." The claim does not define and particularly point out what is a complementary sequence.

The statement in claim 15, "An injectable composition comprising **an agent** according to claim 1," is indefinite because it does not point out which composition; **an agent** is referring to in the claim. The dependent claim should state "**the** agent of claim 1".

Claim 16 is indefinite because it recites "a physiologically vector as defined in claim 1." It is not apparent as to what a physiologically vector is referring to as defined in claim 1.

The statement in claim 17, "... of **an** agent of claim 1 to the patient" is indefinite because it does not point out which composition **an** agent is referring to in the claim. The dependent claim should state "A method for the treatment of a patient using gene therapy.... of **the** agent of claim 1".

Claim 13 is objected to under MPEP 2173.05(h), as using improper Markush group language. The claim recites "wherein the particles are homogeneous **and/or** substantially free of water-soluble material." The terminology "**and/or**" is unacceptable Markush group language. The claim does not define when it is preferred for the particles to be homogenous or substantially free of water-soluble material. Furthermore, in view of the definition of each term, homogeneous and substantially free of water-soluble material are not considered to be from the same species.

Claim 16 recites the limitation "coated particles" on page 15, line 1. There is insufficient antecedent basis for this limitation in the claim. Claim 16 states, "the coated particles and cell-binding component, as defined in claim 1." Claim 1 does not recite coated particles, but claim 1 does recite inorganic particles.

Double Patenting

The non-statutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper time-wise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1-8, 11, and 13-14 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,153,598 (column 8, lines 27-37).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim 1 of the '598 patent encompass ferrite particles, which are free of hydrous oxides chelatable with EDTA, wherein said particles are coated with a biologically tolerable polymer. In addition, claim 2 recites specifically the ferrite particles according to claim 1, wherein said particles carry DNA, RNA, plasmids, ribosomal particles or nucleic acid-binding proteins. In addition claim 3, recites ferrite particles according to claim 1, wherein said particles carry a nerve adhesion molecule. Furthermore, claim 4 recites the ferrite particles according to claim 1, wherein said biologically tolerable polymer is dextran. Thus, the claims of the instant application and the patent are obvious variant of one another.

Claims 1 and 15 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-4 of U.S. Patent No. 6,153,598 (column 8, lines 27-37) in combination with U.S. Patent No. 4,826,823 (IDS, column 8, lines 56-62 and column 9, lines 1-11).

Although the conflicting claims are not identical, they are not patentably distinct from each other because the claim 1 of the '598 patent encompass ferrite particles, which are free of

hydrous oxides chelatable with EDTA, wherein said particles are coated with a biologically tolerable polymer. In addition, claim 2 recites specifically the ferrite particles according to claim 1, wherein said particles carry DNA, RNA, plasmids, ribosomal particles or nucleic acid-binding proteins. In addition claim 3, recites ferrite particles according to claim 1, wherein said particles carry a nerve adhesion molecule. Furthermore, claim 4 recites the ferrite particles according to claim 1, wherein said biologically tolerable polymer is dextran. The difference between the claims of the instant application and the patent is that the instant application encompasses an injectable composition comprising a gene delivery vector described above. However, '823 patent encompasses a method for preparation of an injectable compositions comprising a nucleotide compound (column 8, lines 56-62 and column 9, lines 1-11). One of ordinary skill in the art would have expected the combination of patent '598 and patent '823 would lead to the production of an injectable composition comprising the gene delivery vector set forth above because patent '823 displays that producing a composition for injection is considered routine practice to one skilled in the art. Therefore, it would have been obvious to one of ordinary skill in the art that claimed subject matter of the '598 patent in combination with '823 is an obvious variant of the claims of this instant application.

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Kay Pinkney whose telephone number is (703) 305-3553.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brian Whiteman whose telephone number is (703) 305-0775.

The examiner can normally be reached on Monday through Friday from 7:00 to 4:00 (Eastern Standard Time), with alternating Fridays off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's mentor, primary examiner, Dave Nguyen can be reached at (703) 305-2024.

If attempts to reach the primary examiner by telephone are unsuccessful, the examiner's supervisor, John L. LeGuyader, SPE - Art Unit 1635, can be reached at (703) 308-0447.

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 308-4556.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Brian Whiteman
Patent Examiner, Group 1635
6/26/02

DAVE T. NGUYEN
PRIMARY EXAMINER